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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HELEN GRAS-MASSE, MARC BOSSUS, GUY LIPPENS, JEAN-MICHEL WIERUSZESKI, ANDRE TARTAR, JEAN-GERARD GUILLET, and ISABELLE BOURGAULT-VILLADA

Appeal 2006-2733[1]
Application 09/555,780
Technology Center 1600

Decided: July 21, 2008

Before DEMETRA J. MILLS, LORA M. GREEN, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a composition for inducing an immune response. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] Heard July 8, 2008.

STATEMENT OF THE CASE

Claims 1-7, 9-11, 15, 17-19, and 21-24 stand finally rejected and are the subject of this appeal (App. Br. 2).[2] Claim 1, the only independent claim on appeal, is representative and reads as follows:

> 1. A composition for inducing an immune response, comprising micelles or micro-aggregates wherein each micelle or micro-aggregate comprises:
>
> more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, and
>
> a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit.

The Examiner applies the following documents[3] in rejecting the claims:

Kramer EP 0 230 222 A1 Jul. 29, 1987

G. Stuhler et al., *Antigen organization regulates cluster formation and induction of cytotoxic T lymphocytes by helper T cell subsets*, 94 Proc. Natl. Acad. 622-627 (January 1997).

K. J. Sastry et al., *Identification of T-cell epitopes without B-cell activity in the first and second conserved regions of the HIV Env protein*, 5 AIDS 699-707 (1991).

M. Sugimoto et al., *Enhancement of Carrier-Specific Helper T Cell Function by the Synthetic Adjuvant, N-Acetyl Muramyl-l-Alanyl-d-Isoglutamine (MDP)*, 120 Journal of Immunology 980-982 (1978).

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[2] Supplemental Appeal Brief filed February 28, 2006.

[3] In reviewing this case it appears that none of the references in the appealed rejections has been made part of the official record. When prosecution resumes the Examiner should cite the references on a PTO-Form 892 to place them on the official record.

Y. E. Shapiro et al., *Stabilization of the Peptide Conformation on the Micellar Surface*, 119 Analyst 647-52 (1994).

The following rejections are before us for review:

Claims 1-7, 9, 10, 15, 17-19, and 21-24 stand rejected under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, and Sugimoto (Ans. 4-7).

Claim 11 stands rejected under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, and Kramer (Ans. 8).

Claim 18 stands rejected under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, Kramer, and Shapiro (Ans. 8-10).

OBVIOUSNESS -- STUHLER, SASTRY, AND SUGIMOTO

ISSUE

The Examiner has rejected claims 1-7, 9, 10, 15, 17-19, and 21-24 under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, and Sugimoto[4] (Ans. 4-7). The Examiner cites Stuhler as teaching "a composition for inducing an immune response comprising at least one CTL [(cytotoxic T lymphocyte)] antigenic determinant, and at least one helper T antigenic determinant" (*id.* at 5). The Examiner concedes, however, that:

> Stuhler does not teach conjugating the CTL epitope and the helper T epitope in a micelle composition with palmitic acid

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[4] The Examiner improperly relied on only the abstract of the Sugimoto reference. *See* MPEP § 706.02 ("Citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art."). However, the Examiner cited Sugimoto only to meet a limitation present in claim 9 (*see* Ans. 7). Because we find the limitations of claim 1 dispositive of the obviousness rejections in this appeal, we will not remand the case to the Examiner for a full copy of the Sugimoto article, and we will not further discuss Sugimoto.

> residues, or the composition comprising micelles wherein each micelle comprises more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit and a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit recited in claim 1.

(*Id.*)

The Examiner contends that Sastry meets those limitations because Sastry discloses eliciting cell-mediated immunity with micelle compositions that contain lipopeptides composed of peptides derived from a CTL antigenic determinant (the HIV envelope protein gp 160), and two fatty acid residues attached to terminal lysines on the peptides (Ans. 5-6).

Based on these disclosures the Examiner finds that one of ordinary skill in the art would have been motivated to combine Stuhler's method of eliciting a cytotoxic response with Sastry's micelle composition because Stuhler teaches that linking of cytotoxic T and helper T antigenic determinants "results in successful stimulation of a more complete immune response. More specifically, Stuhler et al. teaches that the organized linkage of CTL and helper T antigenic determinants more efficiently creates a tight cluster on one antigen presenting cell (APC), resulting in more specifically regulated immune responses" (*id.* at 6 (citing Stuhler 626)).

Appellants contend that the Examiner failed to establish a prima facie case of obviousness (App. Br. 9-15). Specifically, Appellants argue that Sastry teaches away from combining the references (*id.* at 9-10), and that Stuhler and Sastry would not have motivated a person of ordinary skill in the art to practice the claimed invention (*id.* at 10-11). Appellants further contend that the combination of Stuhler and Sastry "do[es] not disclose or suggest the claimed element of a composition containing more than one first

lipopeptide and a second lipopeptide," and therefore fails to teach or suggest all of the claims' limitations (*id.* at 15).

Claims 2-7, 9-10, 15, 17-19, and 21-24 all depend ultimately or directly from claim 1, and require all of the elements recited in claim 1. The issue with respect to this rejection, then, is whether the Examiner has established that one of ordinary skill in the art would have considered claim 1 prima facie obvious in view of Stuhler and Sastry.

FINDINGS OF FACT ("FF")

1. Claim 1 recites a composition for inducing an immune response. The composition contains micelles or micro-aggregates. Each micelle or micro-aggregate must contain a lipopeptide comprised of at least one helper T antigenic determinant and at least one lipid unit. Claim 1 also requires each micelle or micro-aggregate to contain "more than one . . . lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit."

2. Stuhler discloses that "[d]esigning vaccination strategies for efficient induction of cytolytic immune responses in humans requires a fundamental knowledge of the immune regulatory properties of the Th [(T helper)] cells" (Stuhler 622). Stuhler therefore "investigated the role of antigen organization in the process of effector CTL generation by Th cell subsets in humans" (*id.* 626).

3. Based on its study, Stuhler found "cluster formation of helper and CTLs and one APC [(antigen presenting cell) to be] a prerequisite for collaboration resulting in specific cytolytic responses. To establish productive interactions, antigens for helper and cytotoxic T cells have to be presented by the same APCs" (*id.*).

3. The Examiner concedes that Stuhler does not disclose compositions having antigenic determinants for both cytotoxic T and helper cells in lipopeptide form as part of a micelle or micro-aggregate (Ans. 5).

4. Sastry discloses that "an effective vaccine against HIV should elicit cell-mediated immunity without an antiviral antibody response" (Sastry 700). To find molecules exhibiting those properties, Sastry discloses that "short peptide sequences selected [from three functionally important regions of the HIV-1 envelope protein gp 160] by established computer programs were synthesized and chemically modified to generate either polymers with disulfide bonds, or micelles with two palmitic acid residues attached to the amino-terminal lysine" (*id.* at 699 (abstract)).

5. To determine the modified peptides' capacity to generate an antibody response, Sastry discloses that:

> Groups of three to five female Balb/c mice 6-8 weeks of age were primed by subcutaneous (s.c.) immunization with 100 μg synthetic peptide in complete Freund's adjuvant (CFA) at 1:1 ratio. Subsequent booster injections were given after 6 and 10 weeks with 50 μg peptide in 1:1 mixture with incomplete Freund's adjuvant (IFA).

(Sastry 700.) "[S]era from individual mice in each group were [then] pooled for determining the presence of anti-peptide antibodies using standard enzyme-linked immunosorbent assay (ELISA) with peroxidase-conjugated goat anti-mouse immunoglobulin G (IgG) as the second antibody" (*id.*).

6. To determine the modified peptides' capacity to generate a T-cell response Sastry discloses that:

> [G]roups of three to five mice were primed with 100 μg synthetic peptide (in 1:1 mixture with CFA) by hind footpad injection. Ten days after immunization, draining popliteal

> lymph-node (PLN) cells from individual mice were harvested; 2 x 10^5 cells in 0.1 ml of Click's medium . . . were cultured in triplicate with 0.1 ml of medium containing various concentrations of synthetic peptide, gp160/gp120, unrelated synthetic peptide or medium alone.

(Sastry 700-701 (citation omitted).) During the final 16-18 hours of culturing, ^{3}H-thymidine was added to the medium and "[t]he cells were harvested onto filter strips for estimating ^{3}H-thymidine incorporation" (*id.* at 701).

7. Sastry discloses that, of the nineteen synthetic peptides studied, "seven induced good T-cell proliferative response in mice representing four major histocompatibility complex haplotypes. None of these seven peptides produced antibodies that could recognize the envelope protein gp160" (Sastry 699 (abstract)).

PRINCIPLES OF LAW

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). "[O]bviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Emphasizing a flexible approach to the obviousness question, the Supreme Court has nonetheless similarly noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity

will be combinations of what, in some sense, is already known." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added); *see also id.* at 1740-41 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

ANALYSIS

Because we are not persuaded that the cited combination of references teaches or suggests all of the limitations in claim 1, we agree with Appellants that the Examiner has not made out a prima facie case of obviousness.

Specifically, claim 1 requires each micelle or micro-aggregate in the claimed composition to comprise "more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit." We therefore interpret claim 1 as requiring each micelle or micro-aggregate particle in the composition to have more than one type of lipopeptide molecule that carries a CTL antigenic determinant.

Thus, when the first lipopeptide comprises only one type of CTL antigenic determinant, each micelle must have at least two lipopeptides with different lipid moieties. Alternatively, if the lipid moieties of the lipopeptides are all the same, as in Sastry (*see* FF 4), each micelle must have at least two lipopeptides with different peptide moieties.

The Examiner argues that Sastry meets these requirements of claim 1 because Sastry synthesized a plurality of lipopeptide constructs, each of which has two lipid moieties attached to it (Ans. 15-16). We are not persuaded by this argument.

As noted above, claim 1 recites a composition comprised of micelles or micro-aggregates, each of which has more than one type of lipopeptide molecule carrying a CTL antigenic determinant. We agree with the Examiner that Sastry discloses preparing more than one type of lipopeptide molecule (*see* FF 4). However, we do not agree with the Examiner that Sastry places any of those different types of lipopeptides molecules, together, into a single micelle, as recited in claim 1.

Specifically, when determining whether its peptides generated antibody or T-cell responses, Sastry discloses that it immunized different groups of mice with "synthetic peptide" (Sastry 700-701 (FF 5, 6)). Therefore, given the apparent disclosure that a single peptide was administered to each group of test mice, and the absence of any explicit disclosure that the immunizing compositions contained more than one type of lipopeptide, we agree with Appellants that one of ordinary skill would have concluded that the compositions Sastry administered to mice contained only one type of lipopeptide, as opposed to the more than one type of lipopeptide required by claim 1.

Thus, we do not agree with the Examiner that Sastry meets the limitation in claim 1 requiring more than one lipopeptide comprised of at least one CTL antigenic determinant and at least one lipid unit. Moreover, the Examiner does not point to any teaching in either of the references, or in the knowledge generally available to one of ordinary skill in the art, that would have prompted one of ordinary skill to include, in Sastry's micelle compositions, more than one type of lipopeptide having at least one CTL antigenic determinant.

We therefore reverse the Examiner's obviousness rejection of claim 1 over Stuhler and Sastry. Because dependent claims 2-7, 9-10, 15, 17-19, and 21-24 all require the element missing from the teachings of Stuhler and Sastry, we reverse the Examiner's rejection of those claims as well.

OBVIOUSNESS -- STUHLER, SASTRY, SUGIMOTO, AND KRAMER

Claim 11 stands rejected under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, and Kramer (Ans. 8).

Claim 11 depends from claim 1 and requires the micelles or micro-aggregates in the composition of claim 1 to comprise one or more lipopeptides having specified amino acid sequences, among them SEQ ID NO: 6 (*see* App. Br. 19). The Examiner concedes that Stuhler, Sastry, and Sugimoto fail to disclose a lipopeptide having the amino acid sequence described in SEQ ID NO: 6 (*id.*). The Examiner cites Kramer as disclosing a peptide having that sequence, "and that it is immunogenic and can be used in detection assays and pharmaceutical compositions" (*id.*). The Examiner finds that "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to use this protein for the immunogenic properties taught by Kramer" (*id.*)

Because of its dependency on claim 1, the composition recited in claim 11 must contain micelles or micro-aggregates that have "more than one . . . lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit," as recited in claim 1. As discussed above, the combination of Stuhler and Sastry fail to teach or suggest that limitation. Because the Examiner does not point to, and we do not see, any disclosure in Kramer that remedies the deficiencies of Stuhler and Sastry in that regard, we reverse the Examiner's rejection of claim 11.

OBVIOUSNESS --

STUHLER, SASTRY, SUGIMOTO, KRAMER, AND SHAPIRO

Claim 18 stands rejected under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, Kramer, and Shapiro (Ans. 8-10).

Claim 18 recites "[a] method according to Claim 17 wherein the dispersing of the lipopeptides dissolved in acetic acid is confirmed by a two-dimensional nuclear magnetic resonance method."

Claim 17, in turn, reads as follows:

> 17. A method for producing micelles or micro-aggregates according to Claim 1, comprising the following steps:
>
> - dispersing each of the constituent lipopeptides in a solution of concentrated acetic acid of about 80% concentration then
>
> - mixing the solutions thus obtained.

The Examiner concedes that none of Stuhler, Sastry, Sugimoto, or Kramer "teaches the use of nuclear magnetic resonance (NMR) in the preparation of micelle compositions," and cites Shapiro to meet that limitation of claim 18 (Ans. 9). The Examiner finds that one of ordinary skill in the art would have been prompted to use "two-dimensional nuclear magnetic resonance (NMR) to analyze and confirm the interaction between the targeted APC and the micelle since Shapiro teaches the use of NMR as a widely known, accurate, and specific method to analyze the micelles and study the peptide conformations and their interactions at the receptor level" (*id.*).

We reverse this rejection as well. Because it ultimately depends from claim 1, the method recited in claim 18 must produce a composition having micelles or micro-aggregates that contain "more than one . . . lipopeptide

comprising at least one CTL antigenic determinant and at least one lipid unit." As discussed above, the combination of Stuhler, Sastry, and Kramer fails to teach or suggest that limitation. Because the Examiner does not point to, and we do not see, any disclosure in Shapiro that remedies the deficiencies of Stuhler, Sastry, and Kramer in that regard, we reverse the Examiner's rejection of claim 18.

SUMMARY

We reverse the Examiner's rejection of claims 1-7, 9, 10, 15, 17-19, and 21-24 under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, and Sugimoto.

We reverse the Examiner's rejection of claim 11 under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, and Kramer.

We reverse the Examiner's rejection of claim 18 under 35 U.S.C. § 103(a) as obvious over Stuhler, Sastry, Sugimoto, Kramer, and Shapiro.

REVERSED

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